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This is a study of the effects of ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), on the osteogenic response to 9 months of exercise training in healthy, premenopausal women, aged 21 to 40 years (N=102). The hypotheses are:

$H1_a$: taking short-acting NDSAIDS before exercise will diminish increases in bone mineral density (BMD) in response to exercise training

$H1_b$: taking short-acting NSAIDS after exercise will not diminish the increases in BMD in response to exercise training

Participants take either ibuprofen (400mg) or placebo capsules before and after each exercise session. Women are randomized to three treatment arms: 1) NSAID before exercise, placebo after exercise (NSAID/placebo; n=34); 2) placebo before exercise, NSAID after exercise (placebo/NSAID; n=34); and 3) placebo before exercise, placebo after exercise (placebo/placebo; n=34). Fifty-three subjects have completed baseline testing and are currently enrolled in the study. Fifteen subjects are presently scheduled for or are undergoing baseline testing. These studies could lead to the development of new strategies to reduce the incidence of, and treatment for, stress fractures that occur in response to vigorous physical activity.

14. SUBJECT TERMS
Exercise, stress fracture, ibuprofen, prostaglandins, bone mineral density, estrogen

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INTRODUCTION:

The primary aim of this randomized, double-blinded, placebo-controlled trial is to determine the effects of NSAID (ibuprofen) use on the osteogenic response to 9 months of exercise training in 102 women. The scientific rationale for this study centers on the knowledge that the osteogenic response to mechanical stress is a prostaglandin (PG)-dependent process and that NSAIDs inhibit PG synthesis. There is evidence that regular NSAID use inhibits the normal bone formation response to mechanical loading, increases risk of fracture, and impairs bone healing. The approved statement of work for this project includes 4 years of recruiting, testing, and training subjects as well as completing sample assays, data analysis, and manuscripts.

BODY:

The major objectives for year 2 were to continue enrollment and performance of tests and procedures and to start assays of biochemical markers on bone turnover and sex hormones. Table 1 is a presentation of the projected and actual enrollment for year 2 of the study. Although the date of award was September 20, 2001, there was a stipulation that work could not commence until IRB and HSRRB review and approval processes were completed. The fully executed agreement was signed on January 31, 2002. Therefore, the expected and actual progression displayed in Table 1 is based on a January 31 start date (i.e., month 1 of Year 2 is February 2003).

The progression of the study is largely determined by the rate of enrollment of subjects and their completion of the intervention. Enrollment is defined as being randomized to study medication and start of the intervention. As shown in Table 1, the number of subjects enrolled in the study is on target for projected enrollment. There are currently 15 subjects undergoing screening and baseline testing for study participation. Based on the anticipated enrollment dates of these subjects, the project is on schedule for enrollment through December 2003. The number of finishers is also on schedule with the projected numbers (Table 2). We projected a dropout rate of 25%, and the actual dropout rate has been 21% (11 of 53). The goal is to have 25 finishers in each of the 3 treatment groups.

Table 3 outlines the success of the various recruitment methods that have been employed. Table 4 illustrates that we are close to projected goals concerning race and ethnicity. New recruitment efforts will continue to target minority populations to increase diversity of enrolled subjects. We do this primarily by advertising in newspapers that target minority populations.

Body composition and bone mass data have been analyzed and computerized for 19 of the current 21 finishers (Table 5). Despite the small sample size, there is already a significant decrease in fat mass and increase in fat-free mass, bone mass, and BMD at several skeletal sites. These preliminary findings indicate that the exercise program is sufficient for generating an osteogenic response, which is critical for determining whether the response is attenuated by NSAID use. At this stage of the project, all indications are that the study is progressing according to schedule. No major changes to the protocol are planned.

The second goal of year 2 of the study was to start assays of biochemical markers of bone turnover and sex hormones by month 8. We recently purchased a new ELISA plate reader for this purpose and the instrument is undergoing preliminary evaluation. Kits to assess biomarkers of bone turnover have been ordered and will be used to establish precision of the assays and to finalize the procedures. We expect to be running study subject samples by the

end of October 2003. Sex hormones assays are being performed as sufficient numbers of participants complete the studies.

In the review of the Annual Report dated October, 2002 (letter to the PI dated July 23, 2003), it was stated that the progress report did not address a weakness identified in the initial review of the protocol (i.e., lack of control over dietary calcium levels and potential confounding effects of subsequent calcium supplementation). The PI has taken the approach she has used in previous studies of having participants complete 3-day food and supplement records at baseline to assess calcium intake. Based on this assessment, supplemental calcium is provided as needed to ensure an intake of ~1200 mg/day. During the data analysis process, baseline calcium intake and average calcium intake during the study will be considered as a potential covariates of the changes in bone mineral density.

KEY RESEARCH ACCOMPLISHMENTS:

Consistent with the Statement of Work, the investigators remain blinded to treatment status for all participants. Therefore, there are no treatment-specific study results to report. The key accomplishments to date have been recruiting, enrolling, and testing subjects, and beginning biomarker assays. All study activities are on schedule, as outlined in the original proposal.

REPORTABLE OUTCOMES:

none

CONCLUSIONS:

Because the investigators remain blinded to treatment status, conclusions cannot yet be drawn.

REFERENCES:

none

APPENDIX COVER SHEET

Tables 1 - 5

APPENDICES:

TABLE 1. Year two projected and actual enrollment

	Month											
	1*	2	3	4	5	6	7	8	***9***	***10***	***11***	***12***
Projected†	33	36	39	42	45	48	51	54	57	60	63	66
Actual†	30	33	36	39	42	43	45	53	***55‡***	***59***	***68***	***68***

* month 1 is February 2003
† numbers represent the cumulative number of enrollees at the end of each month
‡ bold, italicized numbers are projections through January, 2004

TABLE 2. Year two projected and actual finishers and dropouts

	Month											
	1*	2	3	4	5	6	7	8	***9***	***10***	***11***	***12***
Projected finishers	5	7	9	12	14	16	18	21	23	25	27	30
Projected dropouts	1	2	3	3	4	5	6	6	7	8	9	9
Actual finishers	0	6	9	9	9	11	16	21	***23‡***	***25***	***27***	***30***
Actual dropouts	2	4	5	7	8	10	11	11	***11***	***11***	***11***	***11***

* month 1 is February 2003
† numbers represent the cumulative number of finishers and dropouts at the end of each month
‡ bold, italicized numbers are projections through January, 2004

TABLE 3. Recruitment efforts

Recruiting Media	**Number of Phone Screens**	**Number of Orientations**
Flier	63	12
Newspapers	79	21
Campus e-mail	145	51
Word of mouth	38	9
TOTAL	**323**	**95**

TABLE 4. Projected and actual enrollment by ethnicity and race

Race/Ethnic Category	Actual Current Enrollment	% Total	Projected Total Enrollment	% Total
RACE				
American Indian/ Alaskan Native	2	4	1	1
Asian	1	2	3	3
Native Hawaiian/Other Pacific Islander	0	0	0	0
Black/African American	1	2	6	6
White	45	85	92	90
Other/Hispanic	4	8	0	0
Total	**53**		**102**	
ETHNICITY				
Hispanic	5	10	20	20
Non-Hispanic	48	90	82	80
Total	**53**		**102**	

TABLE 5. Body composition, bone mineral content (BMC), and bone mineral density (BMD) of 19 participants before and after 9 months of exercise training.

	before	after	change	p value
Age, yr	33 ± 5			
Height, cm	166 ± 7			
Weight, kg	67.2 ± 10.3	66.2 ± 8.9	-1.0 ± 2.8	0.1305
Fat-free mass, kg	44.4 ± 5.1	45.5 ± 4.8	1.1 ± 1.1	**0.0005**
Fat mass, kg	22.8 ± 7.4	20.7 ± 4.4	-2.1 ± 2.5	**0.0022**
Total body BMC, g	2429 ± 302	2478 ± 332	49 ± 69	**0.0062**
BMD, g/cm^2				
total body	1.189 ± 0.087	1.192 ± 0.085	0.003 ± 0.023	0.6136
lumbar spine	1.155 ± 0.144	1.153 ± 0.135	-0.003 ± 0.021	0.5931
total hip	0.997 ± 0.102	1.010 ± 0.098	0.013 ± 0.014	**0.0006**
femoral neck	0.946 ± 0.119	0.950 ± 0.113	0.004 ± 0.025	0.4921
trochanter	0.779 ± 0.087	0.790 ± 0.091	0.011 ± 0.015	**0.0033**
femoral shaft	1.148 ± 0.122	1.166 ± 0.118	0.017 ± 0.018	**0.0002**